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| 09/857,783 | 11/13/2001 | Itamar Willner | 10980-16001 | 8069 |

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| EXAMINER | |
|---|---|
| LU, FRANK WEI MIN | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1634 | |

DATE MAILED: 01/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/857,783 | WILLNER ET AL. | |
| | Examiner | Art Unit | |
| | Frank W Lu | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *10-22 and 34-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 23-28* is/are rejected.

7)☒ Claim(s) *9 and 29-33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7/03 and 10/01*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election without traverse of Group I, claims 1-11 and 23-33 and species (1) wherein said signal-amplifying agent comprises an enzyme which catalyzes a reaction yielding an insoluble reaction product (claim 9) filed on August 26, 2003 is acknowledged. Therefore, claims 1-9 and 23-33 will be examined.

### *Information Disclosure Statement*

2. The listing of references in the specification is not a proper information disclosure statement. For example, see page 1 of the specification. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

### *Claim Objections*

3. Claim 9 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim 9 can not dependent on any other multiple dependent claim 4 or 6 or 7. See MPEP § 608.01(n). Accordingly, the claim 9 has not been further treated on the merits.

4. Claims 29-33 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claims 29, 31, and 32 can not dependent on another multiple dependent claim

28. See MPEP § 608.01(n). Accordingly, the claims 29-33 have not been further treated on the merits.

5. Claims 1 and 23 are objected to because of the following informality: " a target oligonucleotide" in preamble should be "target oligonucleotides" in order to correspond to the contents of the claims.

6. Claims 3 and 28 are objected to because of the following informality: "the sequence complementary to at least a stably hybridizing portion of the target oligonucleotide" should be "the sequence which is at least complementary to a stable hybridizing portion of the target oligonucleotides".

7. Claim 4 is objected to because of the following informalities: (1) "the verification oligonucleotide is" should be "the verification oligonucleotides are" in order to correspond to verification oligonucleotides in claim 1; and (2) "step (e) of the method comprises" should be "step (e) is performed by".

8. Claim 6 is objected to because of the following informalities: (1) "said verification oligonucleotide is" should be "said verification oligonucleotides are" in order to correspond to verification oligonucleotides in claim 1; and (2) "step (e) comprises" should be "step (e) is performed by".

9. Claim 7 is objected to because of the following informality: "step (e) of the method comprises the following steps" should be "step (e) is performed by".

10. Claim 8 is objected to because of the following informality: "comprising the following step" should be "further comprising a step".

Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-8 and 23-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. Claims 1 and 23 are rejected as vague and indefinite in view of step (a) of the claims because the phrase "a sensor device having a sensing interface carrying capturing oligonucleotides having each a nucleotide sequence complementary in at least a stably hybridizing portion thereof to a first portion of the target oligonucleotides" does not make sense. Does the phrase means a sensor device having a sensing interface carrying capturing oligonucleotides wherein a nucleotide sequence in each of said capturing oligonucleotides is at least complementary to a stable hybridizing portion of a first portion of the target oligonucleotides? Please clarify.

14. Claims 1 and 23 are rejected as vague and indefinite in view of step (b) of the claims because the phrase "verification oligonucleotides having each a nucleotide sequence complementary in at least a stably hybridizing portion thereof to a second portion of the target oligonucleotide" does not make sense. Does the phrase means verification oligonucleotides wherein each of said verification oligonucleotides has a nucleotide sequence which is at least complementary in a stable hybridizing portion of a second portion of the target oligonucleotides? Please clarify.

15. Claims 3 and 28 are rejected as vague and indefinite in view of the phrase "the sequence complementary to at least a stably hybridizing portion of the target oligonucleotide is of about 12 nucleotides". Since claims 1 and 23 have two different sequence (one from capturing oligonucleotides and another from verification oligonucleotides) which are complementary to at least a stably hybridizing portion of the target oligonucleotide, it is unclear that the sequence complementary to at least a stably hybridizing portion of the target oligonucleotide recited in claims 3 and 28 is from a capturing oligonucleotide or is from a verification oligonucleotide. Please clarify.

16. Claim 8 is rejected as vague and indefinite because claim 7 and claim 8 do not correspond each other. According to claim 7, a first recognition agent, a recognition partner, and a second recognition agent forms a complex comprising the first recognition agent, the recognition partner, and the second recognition agent. According to claim 8, newly added recognition partner must bind to the first recognition agent one or more times. If all first recognition agents have bound to the recognition partner as recited in claim 7, how newly added recognition partner could still bind to the first recognition agent as recited in claim 8? Please clarify.

17. Claim 26 is rejected as vague and indefinite because it is unclear what kind of probe can be considered as a microbalance quartz-crystal probe. Do a microbalance quartz-crystal probe mean a probe immobilized on a quartz-crystal microbalance? Note that the specification does not define "a microbalance quartz-crystal probe". Please clarify.

***Claim Rejections - 35 USC § 102***

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

19. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Meade *et al.*, (US Patent No.5, 591,578, published on January 7, 1997).

Meade *et al.*, teach a method of detecting a target sequence in a nucleic acid wherein said target sequence comprises a first target domain and a second target domain adjacent to said first target domain, said method comprising: a) hybridizing a first nucleic acid containing one or multiple electron donor moieties to said first target domain; b) hybridizing a second nucleic acid containing one or multiple electron acceptor moieties to said second target domain, wherein said electron donor and electron acceptor moieties are transition metal complexes covalently attached to the 2' or 3' position of a ribose of the ribose-phosphate backbone of said nucleic acids, wherein said transition metal is selected from the group consisting of Cd, Mg, Cu, Co, Pd, Zn, Fe and Ru; and c) detecting electron transfer between said electron donor and acceptor moieties while said first and second nucleic acids are hybridized to said first and second target domains as an indicator of the presence or absence of said target sequence in said nucleic acid sample (see claims 12 and 13 in columns 24 and 25).

Regarding claims 1 and 2, since one of the first and second nucleic acid probes containing at least one electron transfer moiety is attached via a redox hydrogel to the surface of an electrode (see column 17, lines 9-17), the electrode taught by Meade *et al.*, is a sensor device comprising an electrochemical probe carrying a sensing interface. A nucleic acid probe attached to the electrode taught by Meade *et al.*, (ie., the first nucleic acid probe) is a capturing oligonucleotide as recited in claim 1 and another nucleic acid probe taught by Meade *et al.*, that is not attached to the electrode (ie., the second nucleic acid probe) is a verification oligonucleotide as recited in claim 1. Since Meade *et al.*, teach hybridizing a first nucleic acid containing one or multiple electron donor moieties to said first target domain, hybridizing a second nucleic acid containing one or multiple electron acceptor moieties to said second target domain, and detecting electron transfer between said electron donor and acceptor moieties while said first and second nucleic acids are hybridized to said first and second target domains as an indicator of the presence or absence of said target sequence in said nucleic acid sample (see claims 12 and 13 in columns 24 and 25), steps (a) to (e) of claim 1 is anticipated by Meade *et al.*. Since Meade *et al.*, teach that the electron transfer is detected by use of amperometric, potentiometric or conductometric electrochemical sensors using techniques well known in the art. (see column 17, lines 18-28), claim 2 is anticipated by Meade *et al.*.

Therefore, Meade *et al.*, teach all limitations recited in claims 1 and 2.

20. Claims 1-3, 6, 23-26, and 28 are rejected under 35 U.S.C. 102(e) as being anticipated by Durst *et al.*, (US Patent No. 6,359,752 B1, priority date: May 21, 1998).

Durst *et al.*, teach liposome-enhanced test device and method.

Regarding claims 1, 6, 23, and 24, Durst *et al.*, teach a method for detecting or quantifying an analyte in a liquid test sample comprising: (1) providing a test device comprising: a contact portion on a first absorbent material, a capture portion either on said first absorbent material, or on a second absorbent material in fluid flow contact with said first absorbent material, wherein said capture portion has a first binding material bound to said capture portion, and an electrode array comprising a first conductor having a plurality of fingers, and a second conductor having a plurality of fingers, wherein said fingers of said first conductor are interdigitated with said fingers of said second conductor, said first and second conductors are electrically connected to one another via a voltage source and readout device, and said array is positioned to induce redox cycling of an electroactive marker released from liposomes which migrate beyond said capture portion; (2) applying the test sample to said contact portion; (3) applying a voltage across said conductors, wherein said potential is sufficient to induce redox cycling of said marker; (4) allowing the test sample to migrate from said contact portion through said capture portion; (5) contacting the test sample with a liposome conjugate of liposomes and a second binding material, wherein said liposomes encapsulate an electroactive marker, wherein said second binding material binds with a portion of the analyte, and wherein said first binding material binds with a portion of the analyte other than the portion of said analyte for which said second binding material is selected; (6) incubating the test sample with the conjugate for a time sufficient to permit reaction between any analyte present in the test sample and the second binding material; (7) after said incubating and said allowing, lysing any liposomes which migrate beyond said capture portion to release said marker, whereby said marker undergoes redox cycling induced by said conductors causing current to flow between said first and second

conductors; and (8) detecting the presence or amount of said current and correlating the presence or amount of said current with the presence or amount, respectively, of the analyte in the test sample, wherein the presence or amount of said current is inversely proportional to the presence or amount, respectively, of the analyte in the test sample (see claims 1 and 2 in columns 24-26). Since Durst *et al.*, teach that said analyte is a target nucleic acid molecule, said first binding material is a capture probe selected to at least partially hybridize with a portion of said target nucleic acid molecule, and said second binding material is a reporter nucleic acid molecule selected to at least partially hybridize with a portion of said target nucleic acid molecule other than the portion of said target nucleic acid molecule for which said capture probe is selected and said array is positioned to induce redox cycling of an electroactive marker released from liposomes which migrate beyond said capture portion (see claims 2 and 6 in columns 25 and 26, lines 4-23 in column 12 and Figure 6), Durst *et al.*, disclose a sensor device comprising an electrochemical probe (ie., the electrode array) carrying a sensing interface with a capturing oligonucleotide (ie., the capture probe on said capture portion) as recited in step (a) claims 1 and 23 and claim 24. Since Durst *et al.*, teach contacting the test sample with a liposome conjugate of liposomes and a second binding material, wherein said liposomes encapsulate an electroactive marker, wherein said second binding material (ie., the reporter nucleic acid molecule binds with a portion of the analyte (ie., target nucleic acid molecule) and wherein said first binding material (ie., the capture probe) binds with a portion of the analyte (ie., target nucleic acid molecule) other than the portion of said analyte for which said second binding material is selected, and incubating the test sample with the conjugate for a time sufficient to permit reaction between any analyte present in the test sample and the second

binding material (see claim 2 in column 26, lines 3-23 of column 12 and Figure 6) wherein a marker-encapsulating liposome is a signal amplifying agent as recited in claims 6 and 23 which indirectly binds to the sense interface as recited in step (e) of claim 23, steps (b) to (d) of claims 1 and 23, step (e) of claim 23, and claim 6 are anticipated by Durst *et al.*. Since Durst *et al.*, teach, after said incubating and said allowing, lysing any liposomes which migrate beyond said capture portion to release said marker, whereby said marker undergoes redox cycling induced by said conductors causing current to flow between said first and second conductors, detecting the presence or amount of said current and correlating the presence or amount of said current with the presence or amount, respectively, of the analyte (ie., target nucleic acid molecule) in the test sample, wherein the presence or amount of said current is inversely proportional to the presence or amount, respectively, of the analyte in the test sample (see claim 2 in column 26), Durst *et al.*, disclose to detect the presence of said target oligonucleotides and said verification oligonucleotides (ie., the seconding binding material or the reporter nucleic acid) on the sensing interface by detecting of presence of the signal-amplifying agent (ie., a marker-encapsulating liposome) on the sensing interface as recited in step e) of claim 1, step (f) of claim 23, and claim 6.

Regarding claims 2 and 25, since Durst *et al.*, teach that induction of redox cycling of the electroactive marker released from the liposomes captured in the capture portion is detected by amperometric detector (see column 18, last paragraph and column 19, first paragraph), claims 2 and 25 are anticipated by Durst *et al.*.

Regarding claims 3 and 28, since Durst *et al.*, teach that capture and reporter probes are preferably between 17 and 25 nucleotides long, to provide the requisite specificity while

avoiding unduly long hybridization times and minimizing the potential for formation of secondary structures under the assay conditions (see column 7, lines 19-40), claims 3 and 28 are anticipated by Durst *et al.*.

Regarding claim 26, since the specification does not define "a microbalance quartz-crystal probe", an electrode in the electrode array is considered as a microbalance quartz-crystal probe as recited in claim 26.

Therefore, Durst *et al.*, teach all limitations recited in claims 1-3, 6, 23-26, and 28.

### *Claim Rejections - 35 USC § 103*

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

22. Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Durst *et al.*, (May 21, 1998) as applied to claims 1-3, 6, 23-26, and 28 above, and further in view of Lemar *et al.*, (US Patent No. 6,096,508, filed on August 16, 1995).

The teachings of Durst *et al.*, have been summarized previously, *supra.* Durst *et al.*, teach that the first binding material (ie., the capture probe) is labeled with a tag such as biotin (see column 9, lines 2-11).

Durst *et al.*, do not disclose that verification oligonucleotide recited in claims 1-3 is conjugated to a recognition agent which can specifically bind to a signal-amplifying agent, and step (e) of the method recited in claims 1-3 is performed by contacting the sensing interface with said signal-amplifying agent and detecting the presence of said signal-amplifying agent on the sensing interface as recited in claim 4 wherein said recognition agent is biotin and said signal amplifying agent comprises avidin as recited in claim 5.

Lemar *et al.*, teach method of reducing background in biotin-based assays. Biotin-labeled DNA probes are detected by using a biotin-based detection system such as alkaline phosphatase or horseradish peroxidase as an enzyme conjugated to streptavidin or avidin as a signaling moiety. Suitable substrates for alkaline phosphatase or horseradish peroxidase are added to produce a chromogenic, a fluorogenic or a chemiluminescent reaction with one of above enzymes (see column 5, third paragraph and Example 1 in columns 7 and 8).

Regarding claims 4 and 5, since Durst *et al.*, teach that the first binding material (ie., the capture probe) is labeled with a tag such as biotin, verification oligonucleotide recited in claims 1-3 (ie., the capture probe) is conjugated to a recognition agent (ie., biotin) which can specifically bind to a signal-amplifying agent. Since Lemar *et al.*, teach to detect biotin-labeled

DNA probes using biotin-based detection systems such as alkaline phosphatase or horseradish peroxidase as an enzyme conjugated to streptavidin or avidin as a signaling moiety (ie., a signal-amplifying agent), steps (e1) and (e2) of claim 4 and claim 5 are anticipated by Lemar *et al.*.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have detected the target oligonucleotides recited in claim 1 using a biotin-based detection system such as alkaline phosphatase or horseradish peroxidase as the enzyme conjugated to streptavidin or avidin as a signaling moiety in view of the patents of Durst *et al.*, and Lemar *et al.*. One having ordinary skill in the art would have been motivated to do so because Lemar *et al.*, have successfully used a biotin-based detection system such as alkaline phosphatase or horseradish peroxidase as the enzyme conjugated to streptavidin or avidin to detect biotin-labeled DNA and the simple replacement of one well known detection system (i.e., detecting the presence or amount of the current taught by Durst *et al.*,) from another well known detection system (i.e., the biotin-based detection system taught by Lemar *et al.*,) during the process of performing the method recited in claim 1 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

23. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Durst *et al.*, (May 21, 1998) as applied to claims 1-3, 6, 23-26 and 28 above, and further in view of Lemar *et al.*, (US Patent No. 6,096,508, filed on August 16, 1995).

The teachings of Durst *et al.*, have been summarized previously, *supra.* Durst *et al.*, teach that the first binding material (ie., the capture probe) is labeled with a tag such as biotin (see column 9, lines 2-11).

Durst *et al.*, do not disclose that verification oligonucleotide recited in claims 1-3 comprises a first recognition agent which specifically binds to a recognition partner to form a recognition couple, and step (e) of the method recited in claims 1-3 is performed by contacting said sensing interface with said recognition partner, contacting said sensing interface with a signal-amplifying agent comprising a second recognition agent, which may be the same or different as the first recognition agent, which can also bind to said recognition partner, and detecting presence of said signal-amplifying agent on said sensing interface as recited in claim 7.

Lemar *et al.*, teach method of reducing background in biotin-based assays. Biotin-labeled DNA probes are detected by using a biotin-based detection system such as alkaline phosphatase or horseradish peroxidase as an enzyme conjugated to streptavidin or avidin as a signaling moiety. Suitable substrates for alkaline phosphatase or horseradish peroxidase are added to

produce a chromogenic, a fluorogenic or a chemiluminescent reaction with one of above enzymes (see column 5, third paragraph and Example 1 in columns 7 and 8).

Regarding claim 7, since Durst *et al.*, teach that the first binding material (ie., the capture probe) is labeled with a tag such as biotin, verification oligonucleotide recited in claims 1-3 (ie., the capture probe) comprises a first recognition agent (ie., biotin) which specifically binds to a recognition partner (ie., avidin) to form a recognition couple. Since Lemar *et al.*, teach to detect biotin-labeled DNA probes using biotin-based detection systems such as alkaline phosphatase or horseradish peroxidase as an enzyme conjugated to streptavidin or avidin (ie., a recognition partner), step (e1) of claim 7 is anticipated by Lemar *et al.*. Since Lemar *et al.*, teach that suitable substrates for alkaline phosphatase or horseradish peroxidase are added to produce a chromogenic, a fluorogenic or a chemiluminescent reaction with one of above enzymes in order to detect biotin-labeled DNA probes, suitable substrates for alkaline phosphatase or horseradish peroxidase is a signal-amplifying agent comprising a second recognition agent that can bind to said recognition partner (ie., avidin), steps (e2) and (e3) of claim 7 are anticipated by Lemar *et al.*.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have detected the target oligonucleotides recited in claim 1 using a biotin-based detection system such as alkaline phosphatase or horseradish peroxidase as the enzyme conjugated to streptavidin or avidin in view of the patents of Durst *et al.*, and Lemar *et al.*. One having ordinary skill in the art would have been motivated to do so because Lemar *et al.*, have successfully used a biotin-based detection system such as alkaline phosphatase or horseradish peroxidase as the enzyme conjugated to streptavidin or avidin to detect biotin-

labeled DNA and the simple replacement of one well known detection system (i.e., detecting the presence or amount of the current taught by Durst *et al.,*) from another well known detection system (i.e., the biotin-based detection system taught by Lemar *et al..,*) during the process of performing the method recited in claim 1 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

24. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Durst *et al.,* (May 21, 1998) as applied to claims 1-3, 6, 23-26 and 28 above, and further in view of Okahata *et al.,* (Anal. Chem., 70, 1288-1298, April 1, 1998).

The teachings of Durst *et al.,* have been summarized previously, *supra.*

Durst *et al.,* do not disclose to detect the presence of said signal-amplifying agent on the sensing interface using microgravimetric quartz-crystal microbalance analysis as recited in claim 27.

Okahata *et al.,* teach to measure DNA hybridization using microgravimetric quartz

crystal microbalance analysis wherein an oligonucleotide probe is immobilized on a 27-MHz quartz crystal microbalance (see pages 1288, 1289, 1290, and 1291).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have immobilized the capturing oligonucleotide recited in claim 23 on a 27-MHz quartz crystal microbalance and detected the target oligonucleotides recited in claim 1 using microgravimetric quartz crystal microbalance analysis in view of the prior art of Durst *et al.,* and Okahata *et al.*. One having ordinary skill in the art would have been motivated to do so because Okahata *et al.,* have successfully used microgravimetric quartz crystal microbalance analysis to detect DNA hybridization and the simple replacement of one well known detection system (i.e., detecting the presence or amount of the current taught by Durst *et al.,*) from another well known detection system (i.e., microgravimetric quartz crystal microbalance analysis taught by Okahata *et al..,*) during the process of performing the method recited in claim 1 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

***Conclusion***

25. No claim is allowed.

26. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270 (before January 13, 2004) or 571-272-0746 (after January 13, 2004). The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
PSA
December 24, 2003